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Abstracts

HG-11. INTEGRATIVE MOLECULAR META-ANALYSIS OF 700 PEDIATRIC HIGH GRADE GLIOMA AND DIPG DEFINES WIDESPREAD INTER- AND INTRA-TUMORAL HETEROGENEITY

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Recent molecular profiling studies of paediatric high grade (pHGG) and diffuse intrinsic pontine glioma (DIPG) have refined these tumours into age- and location-based subgroups driven by unique genetic and epigenetic alterations, however individual studies are underpowered to investigate

subgroup-specific events. We have retrieved publicly available genome-wide data from ~560 pHGG/DIPG samples and combined this with ~140 unpublished cases including young adults up to the age of 30 years. We have integrated multiple array-based and sequencing platforms to produce DNA copy number profiles from ~700 tumours, ~500 with clinicopathological and histone H3 annotation, and >300 of which have full somatic sequence information. We identified subgroup-specific genetic alterations co-segregating, or mutually exclusive, with known driving histone mutations. H3.3G34R/V cerebral hemispheric tumours harbour significantly more CNAs and SNVs than other subgroups. These included novel amplified loci at 1p13.3 (KCNA) and a histone cluster at 6p22.2, though lacked key amplified loci such as MYC/MYCIN. H3.1K27M DIPG were distinct from H3.3K27M primarily on the basis of whole arm chromosomal changes (enriched +2, -16q; reduced -17p and a lack of TP53 mutations). H3.3K27M tumours harboured specifically enriched known (7q31.2;MET) and novel amplicons (17p11.2;TOP3A). Integration with mutation data identified subgroup-independent, non-overlapping pathway-level recurrent alterations, such as RTK-PI3K-mTOR, dysregulated in 55% cases and conferring shorter survival in hemispheric, but not other locations. As well as inter-tumoral differences, deeper interrogation of the sequencing data also reveals substantial intra-tumoral heterogeneity. Whilst driving histone H3 mutations were found to be present in 100% of cells, mutations in genes such as PDGFRA and PIK3CA were predominantly found at subclonal levels, and tumours from all locations were inferred to be comprised of multiple subclonal populations, with H3.3G34R/V the most genetically diverse. These data improve our understanding of the underlying biology of pHGG/DIPG, and will provide rational targets for subgroup-specific and –independent therapies.